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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,473	07/30/2002	Ronald de Groot	294-120 PCT/US	4102

7590 08/11/2004

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,473	DE GROOT ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 5/3/04 is made. Claims 39-47 are currently pending.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 39-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39, 44, 45 and 47 are vague and indefinite due to the phrase "has an amino acid sequence *in accordance* with SEQ ID NO:2". The use of the term "in accordance" is vague and indefinite. The claim should be amended to recite that the protein has an amino acid sequence 'consisting of' or 'set forth in' SEQ ID NO:2".

Claims 39, 44 and 47 are vague and indefinite because it is unclear what structures are encompassed by the terms and/or a 'homologous or functionally homologous protein thereof". The terms "homologous" read on as little as one amino acid. Further, the term "functionally" does not provide the structure of the protein. The specification provides no clear definition or description of the structure of a homologous or functionally homologous protein to SEQ ID NO:2 which would still function as a "protease maturation" peptide. Additionally, the

function of the claimed protein has been based solely on sequence homology analysis and not actual testing of the protein. There is no description of which regions need to be maintained in order to conserve function. The terms "homologous" and "functionally homologous" are vague and indefinite terms. Accordingly, the metes and bounds of the claim cannot be understood. Clarification is requested.

Applicants have argued that "homologous" and "functionally homologous protein" are terms of art and define state that "homologous" means "corresponding or similar in position, value and structure or function". This has been fully considered but is not deemed persuasive in overcoming the rejection. The claims, nor the specification, provide a clear definition as to how the structure of the "homologous/functionally homologous" protein is different. The terms "homologous" and "functionally homologous" are objected to by the Office unless they are accompanied by a precise and exact definition as to how the protein structure differs. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim 39 is also rejected under 35 U.S.C. 101 and 112, second paragraph because the claimed invention is vague and indefinite and directed to non-statutory subject matter. Claim 39 fails to state the protein is "isolated" and/or

"purified". The claim reads on a product of nature since it does not specify that the protein is isolated and/or purified. Correction is required.

Claim 39 is vague and indefinite due to the phrase "wherein the composition raises an immune response to streptococcal infections". It is not understood how a protein can raise an immune response to an infection. Do Applicants mean that the composition raises an immune response against *S.pneumoniae* bacteria? It is unclear that use of this protein from *S.pneumoniae* could raise an immune response against other species of *Streptococcus* as they do not all contain this protein.

Claim 44 contains a grammatical error, e.g., "method for preparing of an immunogenic composition". The word "of" should be removed.

The use of the phrases "homologous" or "functionally homologous" in claim 39 was rejected above. Additionally, the use of the term "or a recombinant or synthetic protein thereof" in part (a) of the claim is vague and confusing because it is unclear whether these recombinant or synthetic proteins have SEQ ID NO:2. The claim should actively state that the recombinant or synthetic proteins have SEQ ID NO:2, or this phrase should be deleted since the broad statement "isolating a protease maturation protein of *S.pneumoniae*, wherein the protein has an amino acid as set forth in SEQ ID NO:2' would encompass isolating the protein any of the ways, i.e, naturally, recombinantly, synthetically.

Claim 45 provides for the use of a protease maturation protein, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is

indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 45 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 46 contains a typographical error. The word "raining" should be changed to "raising".

The use of the phrases "homologous" or "functionally homologous" in claim 47 was rejected above.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an immunogenic composition comprising an isolated protease maturation protein of *S.pneumoniae*, wherein the protein has an amino acid sequence as set forth in SEQ ID NO:2" and methods of raising an immune response against *S.pneumoniae* through the administration of said compound, does not reasonably provide enablement for "an immunogenic composition comprising *homologous or functionally*

homologous proteins of an isolated protease maturation protein of *S.pneumoniae* having an amino acid sequence as set forth in SEQ ID NO:2", nor does it enable methods of raising an immune response to a streptococcal infection using said *homologous or functionally homologous proteins*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The breadth of the instant claims contain proteins and amino acid sequences other than what is specified in the sequence disclosure, e.g., functionally homologous or homologous proteins. The specification provides a general statement that homologous or functionally homologous sequences are included; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The instant claims are drawn to proteins which are homologous or vary from a given protein; i.e., equivalent sequences,

homologous sequences, fragments, etc.. The position and individual amino acid residues in peptide antigen-antibody interactions is extremely important. Selective point mutation to one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the "native" protein on the *S.pneumoniae* bacteria, and be ineffective in "treating" infections caused by *S.pneumoniae*. The specification and claims recite homologous and/or functionally homologous proteins to SEQ ID NO:2 yet provide no teaching or guidance as to the structure of these proteins or how to isolate/make them. It is unclear which portions of the sequence are required to retain function.

There are no results provided from active immunizations, let alone challenge experiments. The specification provides teaches how to make hyperimmune serum through injection of the full-length protein set forth in SEQ ID NO:2. In vitro assays which demonstrate the serum's opsonophagocytic

activity are provided. However, no experiments, results or methods are which demonstrate that any fragments or homologous proteins are able to successfully raise an immune response to S.pneumoniae. There are no results from active immunization experiments. The specification fails to teach the location, if any, of immunoprotective epitopes. Often times it takes more than one epitope to provide immune protection. With respect to homologous or equivalent sequences, as stated above, no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced is provided. The enablement and written description in this case only sets forth SEQ ID NO:2. With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed homologous or functionally homologous proteins and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate enablement and written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed homologous and functionally homologous proteins. As stated in the 112 second paragraph rejection above, it is unclear what structures are considered to represent a homologous or functionally homologous protein. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

5. Claims 39-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunsch et al (WO 98/18930).

Kunsch et al teach antigens and vaccines to prevent or attenuate infections caused by bacteria of the *Streptococcus* genus and *S.pneumoniae* in particular. See abstract and page 115. The vaccine encompasses a polypeptide or fragment thereof contained in Table 1. Table 1 discloses a polypeptide which has 213 identical amino acids to Applicants' SEQ ID NO:2 which is 322 amino acids in length. See attached sequence alignment. The instant claims encompass fragments and use the open language "comprising". Accordingly, the polypeptide and/or its fragments to be used in the vaccines read on the instant claims. A protein with this large of a conserved region would inherently be homologous and/or functionally homologous. This protein and its fragments would be expected to raise a very similar or homologous immune response. The reference teaches that the vaccine may be prepared with a carrier and/or an adjuvant and is suitable to elicit protective antibodies in the vaccinated animal. See pages 4-5. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function. Recombinant methods of producing the protein and/or epitope-bearing portions are also taught. See page 3, line 32- page 33, line 5. Applicants should limit their claims to the full-length sequence of SEQ ID NO:2.

6. Claims 39-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Black et al (US 6,348,328 B1).

Black et al teach a polypeptide which has 48 identical amino acids to Applicants' SEQ ID NO:2 and a 97% local similarity. See attached sequence alignment. Black et al teach that the polypeptide is from *S.pneumoniae*. It is taught that the proteins or their fragments may be used in pharmaceutical compositions or vaccines along with a carrier and or an adjuvant to treat infections caused by the bacteria. The manufacture of such medicaments is also taught. See columns 16-17. See column 20, lines 33-41 for vaccine teachings. Recombinant production of the polypeptides is also taught. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function. The instant claims include "homologous" polypeptides. This large fragment taught by Black is a 'homologous' sequence. Applicants have amended the claims from the term "immunogenic fragment", but the claims still read on these fragments. The specification provides no clear description of what structures are required for a protein to be considered 'homologous'. The specification does teach that fragments of 5-8 amino acids in length and preferably 10-15 amino acids in length are included in the scope of invention. Blacks fragments anticipate the claims.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

Jennifer Graser
Primary Examiner
Art Unit 1645

8/9/04